

The Seminal Literature of Anthrax Research

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A chronically weak area in research papers, reports, and reviews is the complete identification of seminal background documents that formed the building blocks for these papers. A method for systematically determining these seminal references is presented. Citation-Assisted Background (CAB) is based on the assumption that seminal documents tend to be highly cited. Application of CAB to the field of Anthrax research is presented. While CAB is a highly systematic approach for identifying seminal references, it is not a substitute for the judgment of the researchers, and serves as a supplement.

Keywords Anthrax; *Bacillus anthracis*; Zoonotic; Vaccine; Text Mining; Citation-Assisted Background; Literature Survey

INTRODUCTION

Research is a method of systematically exploring the unknown to acquire knowledge and understanding. Efficient research requires awareness of all prior research and technology that could impact the research topic of interest, and builds upon these past advances to create discovery and new advances. The importance of this awareness of prior art is recognized throughout the research community. It is expressed in diverse ways, including requirements for Background sections in journal research articles, invited literature surveys in targeted research areas, and required descriptions of prior art in patent applications.

For the most part, development of Background material for any of the above applications is relatively slow and labor intensive, and limited in scope. Background material development

usually involves some combination of manually sifting through outputs of massive computer searches, manually tracking references through multiple generations, and searching ones own records for personal references. The few studies that have been done on the adequacy of Background material in documents show that only a modest fraction of relevant material is included (MacRoberts and MacRoberts 1989; 1996; Liu 1993; Calne and Calne 1992; Shadish et al. 1995; Moravcsik and Murugesan 1975).

In particular, an analysis of Medline papers on the hemodynamic response to orotracheal intubation showed that recognized deficiencies in research method were not acknowledged. The authors recommended that, when submitting work for publication, investigators should provide evidence of how they searched for previous work (Smith and Goodman 1997).

Another specific example was provided by MacRoberts and MacRoberts (1997). Replicating their earlier work in a journal on genetics that indicated that only 30% of influences evident in text are reflected in a paper's references, the text of an issue of Sida was studied by the MacRoberts to extract influences of previous work evident therein. Influences they judged present in the text appeared in the references only 29% of the time.

Typically missing from standard Background section or review article development, as well as in the specific examples cited above, is a systematic approach for identifying the key documents and events that provided the groundwork for the research topic of interest. The present paper presents such a systematic approach for identifying the key documents, called Citation-Assisted Background (CAB). The next section describes the CAB concept, and provides an outline of its operation, with an application to the area of Anthrax research.

CONCEPT DESCRIPTION

The CAB concept (Kostoff and Shlesinger 2004) identifies the seminal Background documents for a research area using citation analysis. CAB rests on the assumption that a document

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that is a significant building block for a specific research area will typically have been referenced positively by a substantial number of people who are *active researchers in that specific area*. Implementation of the CAB concept then requires the following steps:

- The research area of interest must be defined clearly
- The documents that define the area of interest must be identified and retrieved
- The references most frequently used in these documents must be identified and selected
- These critical references must be analyzed, and integrated in a cohesive narrative manner to form a comprehensive Background section or separate literature survey

These required steps are achieved in the following manner.

1. The research topic of interest is defined clearly by the researchers who are documenting their study results. For example, consider the topic of Anthrax. In a recent text mining study of Anthrax, the topical area was defined to include Anthrax research, clinical issues, and terrorist-related issues.
2. The topical definition is sharpened further by the development of a literature retrieval query. In the text mining study mentioned above, the literature retrieval query was “anthrax OR anthracis OR anthraxin.” Because of the relatively sharp focus of Anthrax, the query is quite small. Other text mining queries for broader literatures have required hundreds of query terms (Kostoff et al. 1998, 2000, 2004).
3. The query is entered into a database search engine, and documents relevant to the topic are retrieved. In the Anthrax text mining study mentioned above, 1834 documents were retrieved from the Web version of the Science Citation Index (SCI) for the years 1991–late 2003. The SCI was used because it is the only major research database to contain references, in a readily extractable format.
4. These documents are combined to create a separate database, and all the references contained in these documents are extracted. Identical references are combined, the number of occurrences of each reference is tabulated, and a table of references and their occurrence frequencies is constructed. In the anthrax text mining study, 25258 separate references were extracted and tabulated. Table 1 contains the ten highest frequency (most cited) references extracted from the Anthrax database.

Two frequencies are computed for each reference, but only the first is shown in Table 1. The frequency shown in the rightmost column is the number of times each reference was cited *by the 1834 records in the retrieved database only*. This number reflects the importance of a given reference to the *specific discipline of Anthrax*. The second frequency number (not shown) is the total number of citations the reference received from all sources, and reflects the importance of a given reference to *all the fields of*

TABLE 1
Most highly cited documents

Author	Year	Source	Vol	Page	#CIT
Inglesby TV	1999	JAMA-J Am Med Assoc	281	1735	173
Leppia SH	1982	P Natl Acad Sci USA	79	3162	164
Friedlander AM	1986	J Biol Chem	261	7123	158
Duesbery NS	1998	Science	280	734	150
Meselson M	1994	Science	266	1202	143
Dixon TC	1999	New Engl J Med	341	815	137
Green BD	1985	Infect Immun	49	291	111
Petosa C	1997	Nature	385	833	105
Mikesell P	1983	Infect Immun	39	371	99
Milne JC	1994	J Biol Chem	269	20607	97

science that cited the reference. This number is obtained from the citation field or citation window in the SCI. In CAB, only the first frequency is used, since it is topic-specific. Using the first discipline-specific frequency number obviates the need to normalize citation frequencies for different disciplines (due to different levels of activity in different disciplines), as would be the case if total citation frequencies were used to determine the ordering of the references.

Before presenting a specific implementation algorithm for the Anthrax application, a few caveats will be discussed. First, listing and selection of the most highly cited references are dependent on the comprehensiveness and balance of the total records retrieved. Any imbalances (from skewed databases or incorrect queries) can influence the weightings of particular references, and result in some references exceeding the selection threshold where not warranted, and others falling below the threshold where not warranted.

Second, it is important that the query used for record retrieval be extensive (Khan and Khor 2004; Harter and Hert 1997; Kantor 1994), as was shown for the anthrax application. The query needs to be checked for precision and recall, which becomes complicated when assumptions of binary relevance and binary retrieval are relaxed (Della Mea and Mizzaro 2004). There are a multitude of issues to be considered when evaluating queries and their impact on precision and recall. A recent systems analytic approach to analyzing the information retrieval process concludes that, for completeness, the interaction of the Environment and the information retrieval system must be considered in query development (Kagolovsky and Moehr 2004). The first author's experiences (with the four studies done so far with CAB, including the study reported in this paper) have shown that modest query changes may substitute some papers at the citation selection threshold, but the truly seminal papers have citations of such magnitude that they are invulnerable to modest query changes. For this reason, the cutoff threshold for citations has been, and should be, set slightly lower, to compensate for query uncertainties.

Third, there may be situations where at least minimal citation representation is desired from each of the major technical thrust areas in the documents retrieved. In this case, the retrieved documents could be clustered into the major technical thrust areas, and the CAB process could be performed additionally on the documents for each cluster. The additional references identified with the cluster-level CAB process, albeit with lower citations than from the aggregated non-clustered CAB process, would then be added to the list obtained with the aggregated CAB process. The first author has not found this cluster-level CAB process necessary for any of the disciplines studied with CAB so far.

Fourth, there may be errors in citation counts due to references errors, and the subsequent fragmenting of a reference's occurrence frequency metric into smaller metric values. Care needs to be taken in insuring that a given reference is not fissioned into multiple large fragments that are not subsequently combined.

Fifth, the CAB approach is most accurate for recent references, and its accuracy drops as the references recede into the distant past. This results from the tendency of authors to reference more recent documents and, given the restricted real estate in journals, not reference the original documents. To get better representation, and more accurate citation numbers, for early historical documents, the more recent references need to be retrieved, collected into a database, and have their references analyzed in a similar manner (essentially examining generations of citations).

Sixth, high citation frequencies are not unique to seminal documents only; different types of references can have high citation frequencies. Documents that contain critical research advances, and were readily accessible in the open literature, tend to be cited highly, and represent the foundation of the CAB approach. Application of CAB to three technical research areas so far (in addition to the present Anthrax study) shows that this type of document is predominant in the highly cited references list. Books or review articles also appear on the highly cited references list. These documents do not usually represent new advances, but rather are summaries of the state of the art (and its Background) at the time the document was written. These types of documents are still quite useful as Background material. Finally, documents that receive large numbers of citations highly critical of the document could be included in the list of highly cited documents. In three studies so far, the first author has not identified such papers in the detailed development of the Background.

Additionally, one of the three application studies concerns high-speed compressible flow, a discipline in which the first author worked decades ago. Using the CAB approach, the first author found that all the key historical documents with which he was familiar were identified, and all the historical documents identified appeared to be important. Thus, for that data point at least, the weaknesses identified above (imbalances, undervaluing early historical references, unwanted highly cited docu-

ments) did not materialize. To insure that any critical documents were not missed because of imbalance problems, the threshold was set a little bit lower to be more inclusive.

The converse problem to multiple types of highly cited references, some of which may not be the seminal documents desired, is influential references that do not have substantial citation frequencies. If the authors of these references did not publish them in widely and readily accessible forums, or if they do not contain appropriate verbiage for optimal query accessibility, then they might not have received large numbers of citations. Additionally, journal or book space tends to be limited, with limited space for references. In this zero-sum game for space, research authors tend to cite relatively recent records at the expense of the earlier historical records. Also, extremely recent but influential references have not had the time to accumulate sufficient citations to be listed above the selection threshold on the citation frequency table. Methods of including these influential records located at the wings of the temporal distribution will be described in the following implementation section. Inclusion of the references that were not widely available when published is more problematic, and tends to rely on the Background developers' personal knowledge of these documents, and their influence.

CONCEPT IMPLEMENTATION

To identify the total candidate references for the Background section, a table similar in structure to Table 1, but containing all the references from the retrieved records, is constructed. A threshold frequency for selection can be determined by arbitrary inspection (i.e., a Background section consisting of 150 key references is arbitrarily selected). The first author has found a dynamic selection process more useful. In this dynamic process, references are selected, analyzed, and grouped based on their order in the citation frequency table until the resulting Background is judged sufficiently complete by the Background developers.

To insure that the influential documents at the wings of the temporal distribution are included, the following total process is used. The reference frequency table is ordered by inverse frequency, as above, and a high value of the selection frequency threshold is chosen initially. Then, the table is re-ordered chronologically. The early historical documents with citation frequencies substantially larger than those of their contemporaries are selected, as are the extremely recent documents with citation frequencies substantially larger than those of their contemporaries. By contemporaries, it is meant documents published in the same time frame, not limited to the same year. Then, the dynamic selection process defined above is applied to the early historical references, the intermediate time references (those falling under the high frequency threshold), and the extremely recent references.

Table 2 contains the final references selected for the Anthrax Background survey. The first reference listed, Koch's 1876 paper, had many more citations (ten) than any papers published in the 1860s or 1870s. In fact, there were half a dozen papers

TABLE 2
Seminal documents selected for inclusion in background

Author	Year	Source	Vol	Page	#CIT
Koch R	1876	Beitr Biol Pflanz	2	277	10
Pasteur L	1881	C R Acad Sci Agr Bul	92	429	15
Sterne M	1939	J Vet Sci Anim Ind	13	307	24
Gladstone GP	1946	Br J Exp Pathol	27	394	14
Smith H	1954	Nature	173	869	31
Belton FC	1954	Brit J Expt Patholog	35	144	26
Smith H	1955	Brit J Exp Pathol	36	460	22
Henderson DW	1956	J HYG	54	28	34
Ross JM	1957	J Pathol Bacteriol	73	485	38
Albrink WS	1960	Am J Pathol	36	457	21
Stanley JL	1961	J Gen Microbiol	26	49	55
Brachman PS	1962	Am J Public Health	52	632	69
Beall FA	1962	J Bacteriol	83	1274	58
Smith H	1962	J Gen Microbiol	29	517	21
Puziss M	1963	Appl Microbiol	11	330	30
Laforce FM	1969	Arch Environ Health	18	798	20
Laemmli UK	1970	Nature	227	680	42
Vanness GB	1971	Science	172	1303	21
Miller JH	1972	Expt Mol Genetics			33
Sanger F	1977	P Natl Acad Sci USA	74	5463	22
Kaneko T	1978	Microbiol Immunol	22	639	37
Gill DM	1978	Bacterial Toxins Cel		291	26
Seki T	1978	Int J Syst Bacteriol	28	182	23
Brachman PS	1980	Ann NY Acad Sci	353	83	51
Leppla SH	1982	P Natl Acad Sci USA	79	3162	164
Mikesell P	1983	Infect Immun	39	371	99
Vodkin MH	1983	Cell	34	693	45
Ristroph JD	1983	Infect Immun	39	483	30
Leppla SH	1984	Adv Cyclic Nucl Prot	17	189	54
Hambleton P	1984	Vaccine	2	125	44
Ezzell JW	1984	Infect Immun	45	761	34
Green BD	1985	Infect Immun	49	291	111
Uchida I	1985	J Gen Microbiol	131	363	55
Obrien J	1985	Infect Immun	47	306	32
Friedlander AM	1986	J Biol Chem	261	7123	158
Turnbull PCB	1986	Infect Immun	52	356	54
Ivins BE	1986	Infect Immun	54	537	52
Little SF	1986	Infect Immun	52	509	46
Welkos SL	1986	Infect Immun	51	795	43
Ivins BE	1986	Infect Immun	52	454	42
Robertson DL	1986	Gene	44	71	34
Leppla SH	1988	Method Enzymol	165	103	79
Welkos SL	1988	Gene	69	287	74
Gordon VM	1988	Infect Immun	56	1066	70
Ivins BE	1988	Eur J Epidemiol	4	12	39
Escuyer V	1988	Gene	71	293	38
Robertson DL	1988	Gene	73	363	35
Mock M	1988	Gene	64	277	34
Makino S	1988	Mol Microbiol	2	371	33
Leppla SH	1988	Bacterial Protein TO		111	33
Turnbull PCB	1988	Med Microbiol Immun	177	293	32
Singh Y	1989	J Biol Chem	264	19103	67
Sambrook J	1989	Mol Cloning Lab Manu			62

(Continued)

TABLE 2
Seminal documents selected for inclusion in background (*Continued*)

Author	Year	Source	Vol	Page	#CIT
Makino S	1989	J Bacteriol	171	722	61
Blaustein RO	1989	P Natl Acad Sci USA	86	2209	59
Bragg TS	1989	Gene	81	45	53
Singh Y	1989	J Biol Chem	264	11099	44
Bhatnagar R	1989	Infect Immun	57	2107	39
Bartkus JM	1989	Infect Immun	57	2295	32
Cataldi A	1990	Mol Microbiol	4	1111	34
Labruyere E	1990	Biochemistry-US	29	4922	33
Ivins BE	1990	Infect Immun	58	303	30
Pezard C	1991	Infect Immun	59	3472	95
Leppla SH	1991	Sourcebook Bacterial		277	89
Escuyer V	1991	Infect Immun	59	3381	72
Ash C	1991	Int J Syst Bacteriol	41	343	72
Turnbull PCB	1991	Vaccine	9	533	68
Quinn CP	1991	J Biol Chem	266	20124	40
Koehler TM	1991	Mol Microbiol	5	1501	38
Singh Y	1991	J Biol Chem	266	15493	34
Klimpel KR	1992	P Natl Acad Sci USA	89	10277	96
Turnbull PCB	1992	J Appl Bacteriol	72	21	46
Ivins BE	1992	Infect Immun	60	662	38
Hanna PC	1992	Mol Biol Cell	3	1269	37
Molloy SS	1992	J Biol Chem	267	16396	37
Novak JM	1992	J Biol Chem	267	17186	35
Arora N	1992	J Biol Chem	267	15542	35
Hanna PC	1993	P Natl Acad Sci USA	90	10198	94
Friedlander AM	1993	J Infect Dis	167	1239	78
Abramova FA	1993	P Natl Acad Sci USA	90	2291	69
Arora N	1993	J Biol Chem	268	3334	53
Milne JC	1993	Mol Microbiol	10	647	51
Uchida I	1993	J Bacteriol	175	5329	48
Friedlander AM	1993	Infect Immun	61	245	39
Pezard C	1993	J Gen Microbiol	139	2459	35
Thorne CB	1993	Bacillus Subtilis OT		113	31
Drobniewski FA	1993	Clin Microbiol Rev	6	324	30
Meselson M	1994	Science	266	1202	143
Milne JC	1994	J Biol Chem	269	20607	97
Klimpel KR	1994	Mol Microbiol	13	1093	85
Hanna PC	1994	Mol Med	1	7	52
Koehler TM	1994	J Bacteriol	176	586	46
Singh Y	1994	J Biol Chem	269	29039	36
Arora N	1994	Infect Immun	62	4955	32
Laforce FM	1994	Clin Infect Dis	19	1009	31
Henderson I	1994	Int J Syst Bacteriol	44	99	30
Sirard JC	1994	J Bacteriol	176	5188	30
Milne JC	1995	Mol Microbiol	15	661	42
Harrell LJ	1995	J Clin Microbiol	33	1847	39
Dai ZH	1995	Mol Microbiol	16	1171	38
Leppla SH	1995	Handb Nat T	8	543	34
Etiennetoumelin I	1995	J Bacteriol	177	614	33
Leppla SH	1995	Bacterial Toxins Vir		543	30
Ramisse V	1996	FEMS Microbiol Lett	145	9	34
Andersen GL	1996	J Bacteriol	178	377	34

(Continued on next page)

TABLE 2
Seminal documents selected for inclusion in background (*Continued*)

Author	Year	Source	Vol	Page	#CIT
Petosa C	1997	Nature	385	833	105
Franz DR	1997	JAMA-J Am Med Assoc	278	399	69
Keim P	1997	J Bacteriol	179	818	53
Christopher GW	1997	JAMA-J Am Med Assoc	278	412	45
Torok TJ	1997	JAMA-J Am Med Assoc	278	389	40
Zilinskas RA	1997	JAMA-J Am Med Assoc	278	418	36
Duesbery NS	1998	Science	280	734	150
Vitale G	1998	Biochem Bioph Res Co	248	706	75
Pile JC	1998	Arch Intern Med	158	429	47
Hanna P	1998	Curr Top Microbiol	225	13	41
Wesche J	1998	Biochemistry-US	37	15737	39
Benson EL	1998	Biochemistry-US	37	3941	36
Patra G	1998	J Clin Microbiol	36	3412	34
Jackson PJ	1998	P Natl Acad Sci USA	95	1224	32
Inglesby TV	1999	JAMA-J Am Med Assoc	281	1735	173
Dixon TC	1999	New Engl J Med	341	815	137
Henderson DA	1999	JAMA-J Am Med Assoc	281	2127	54
Pellizzari R	1999	FEBS Lett	462	199	52
Okinaka RT	1999	J Bacteriol	181	6509	43
Friedlander AM	1999	JAMA-J Am Med Assoc	282	2104	42
Guidirontani C	1999	Mol Microbiol	31	9	41
Miller CJ	1999	Biochemistry-US	38	10432	31
Shafazand S	1999	Chest	116	1369	31
Henderson DA	1999	Science	283	1279	30
Helgason E	2000	Appl Environ Microb	66	2627	69
Keim P	2000	J Bacteriol	182	2928	55
Inglesby TV	2000	JAMA-J Am Med Assoc	283	2281	55
Vitale G	2000	Biochem J 3	352	739	38
*CDCP	2000	MMWR-Morbid Mortal W	49	1	23
Elliott JL	2000	Biochemistry-US	39	6706	20
Khan AS	2000	Lancet	356	1179	20
Turnbull PCB	2000	Curr Opin Infect Dis	13	113	20
Jernigan JA	2001	Emerg Infect Dis	7	933	96
Bradley KA	2001	Nature	414	225	66
Mock M	2001	Annu Rev Microbiol	55	647	49
CDCP	2001	MMWR-Morbid Mortal W	50	909	48
Pannifer AD	2001	Nature	414	229	46
Dennis DT	2001	JAMA-J Am Med Assoc	285	2763	42
Swartz MN	2001	New Engl J Med	345	1621	39
Sellman BR	2001	Science	292	695	34
Mourez M	2001	Nat Biotechnol	19	958	32
Borio L	2001	JAMA-J Am Med Assoc	286	2554	31
Arnon SS	2001	JAMA-J Am Med Assoc	285	1059	30
*CDCP	2001	MMWR-Morbid Mortal W	50	889	30
Bush LM	2001	New Engl J Med	345	1607	27
*CDCP	2001	MMWR-Morbid Mortal W	50	941	27
Mayer TA	2001	JAMA-J Am Med Assoc	286	2549	24
Grinberg LM	2001	Modern Pathol	14	482	23
Inglesby TV	2002	JAMA-J Am Med Assoc	287	2236	59
Barakat LA	2002	JAMA-J Am Med Assoc	287	863	23
Drum CL	2002	Nature	415	396	21
Read TD	2003	Nature	423	81	8
Scobie HM	2003	P Natl Acad Sci USA	100	5170	7

published between 1528 and 1876 that had two citations each, and these were the closest to Koch's paper. This is a graphic example of how we interpret a paper's having substantially more citations than its contemporaries.

These results were examined by the authors. They judged that all papers in the table were relevant for a Background section, or review paper. Due to space considerations, not all papers listed will be included in the historical narrative shown in the next section.

The analysis and discussion above have focused on the *contents* of the Background; i.e., which documents should be included. In some cases, the Abstracts of the seminal references have been retrieved and clustered, to produce a *structure* for the Background. Thus, the CAB approach can be used to determine both the content and structure of the Background section. Again, CAB does not exclude content and structure determinations by the experts. CAB can be viewed as the starting point for content and structure determination, upon which the experts can build with their own insights and experience.

While the CAB approach is systematic, it is not automatic. Judgment is required to determine when an adequate number of references has been selected for the Background, and further judgment is required to analyze, group, and link the references to form a cohesive Background section. Additionally, the highly influential references that were not highly cited due to insufficient dissemination should be included by the Background developers, if they know of such documents. CAB is not meant to replace individual judgment or specification of Background material. CAB is meant to augment individual judgment and reference selection, as reflected in its name of Citation-Assisted.

ANTHRAX LITERATURE REVIEW

Overview

Anthrax is primarily a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis*. The ability to form spores permits the organism to survive environmental conditions that kill most other bacteria. Dormant spores present in the soil infect mainly herbivores (and carnivores that eat the herbivores). Spores can infect humans who come in contact with the infected animal or its products (e.g., meat, hides, wool, etc.) (Boutiba-Ben Boubaker and Ben Redeheb 2001; Jedrzejewski 2002; Mock and Fouet 2001).

Anthrax has had a long history. It was thought to be responsible for the 5th and 6th plagues in Egypt that were described in the Old Testament. Subsequently, there were numerous descriptions of a disease resembling anthrax in both animals and humans in the literature of the Greeks, Romans, and Hindus (Dirckx 1981). In the Middle Ages, anthrax swept across Europe, killing large numbers of humans and animals (Turnbull 2002). With the industrialization of Europe, smaller outbreaks of anthrax began to occur in factories where imported animal hides and hair were processed (Hugh-Jones 1999). The association of anthrax with wool led to the name woolsorters disease.

The study of anthrax led to the development of modern bacteriology, serology, and immunology. The microorganisms were first seen in 1863 by Davaine, who proved their infectivity. For an eloquent description of Davaine's discoveries, see the reply of Pasteur to a paper by Koch in an Extract from The Scientific Review Paris of 20 January 1883. In 1876, Robert Koch isolated the bacillus in pure culture in the vitreous of cow's eyes and established Koch's postulates (Koch 1876). Shortly thereafter, Louis Pasteur demonstrated protection against anthrax following immunization of sheep with a live attenuated bacterial vaccine (Pasteur 1881). It wasn't until 1954 that a toxin was shown to be responsible for the death of infected animals (Smith and Keppie 1954).

Anthrax is still enzootic in most developing countries and it occurs sporadically in many other countries (Hugh-Jones 1999). West Africa is the most affected area of the world (Davies 1982; Hugh-Jones 1999). Anthrax remains a significant problem in other parts of Africa, Central America, Spain, Greece, Turkey, Albania, Romania, Central Asia, and the Middle East (Bales et al. 2002; Cieslak and Eitzen 1999; Hugh-Jones 1999; Kaya et al. 2002; Schmidt and Kaufman 2002).

Between 20,000 and 100,000 cases of human anthrax are estimated to occur worldwide annually (Cieslak and Eitzen 1999). Because anthrax remains a problem in developing countries, animal products imported from these areas continue to pose a risk. Human cases occur infrequently in economically advanced countries, where animal anthrax is under control. The incidence of infection has been reduced dramatically by vaccination of high-risk people and animals, along with improvements in industrial hygiene (Jefferson et al. 2000; Turner et al. 1999). For example, in the United States, there were about 120 cases per year in the early part of the 20th century, which declined to less than 1 case per year during the 1990s.

B. anthracis is an aerobic or facultatively anaerobic, large, square-ended Gram-positive rod with a centrally located ellipsoidal to cylindrical spore. Recent taxonomic studies indicate that *B. anthracis* is closely related to *Bacillus cereus* and *Bacillus thuringiensis* and these three microorganisms should be considered a single species (Helagson et al. 2000). Furthermore, it is likely that *B. anthracis* is a lineage of *B. cereus*, which has implications for virulence and for horizontal gene transfer within this group or organisms (Helagson 2000). Chains of virulent cells of *B. anthracis* are usually surrounded by a capsule; avirulent strains are often unencapsulated. Sporulation occurs in the soil and on culture medium but not in living tissue, unless exposed to air. Spores enter the human host through breaks in the skin, inhalation, or by ingestion, where they are engulfed by macrophages or other phagocytic cells. The spores germinate within the phagocytic cell forming encapsulated vegetative cells that produce several extracellular protein toxins (Brossier et al. 1998; Brossier et al. 2000; Mourez et al. 2002).

There are different clinical forms of anthrax, which reflect the route by which the spores entered the host. The vast majority of cases of naturally acquired anthrax (ca. 95%) are the cutaneous

form, followed by the inhalational, gastrointestinal and other rare forms. Cutaneous anthrax begins as a small, painless, but often pruritic papule. As the papule enlarges, it becomes vesicular and, within 2 days, ulcerates to form a distinctive black (hence the name of the disease) eschar, with surrounding edema. The case fatality rate of untreated cutaneous anthrax can be as high as 25%. Inhalational anthrax begins with an upper-respiratory flu-like syndrome, which after a few days takes a fulminant course, manifested by dyspnea, cough, chills, and a high-grade bacteremia. Massive hilar adenopathy and mediastinal hemorrhage is evident in chest x-rays as a widening of the hilum, followed by massive widening of the mediastinum with clear and sharp borders (Vessal 1975). If not recognized and treated early, nearly all patients with this disease will die within several days. Gastrointestinal anthrax probably occurs more frequently than realized. Most cases are recognized after death because clinical diagnosis is extremely difficult. Many mild cases probably escape detection. In gastrointestinal anthrax there is mucosal ulceration, mesenteric adenitis, ascites, cholera-like diarrhea, and moderate to severe fever with chills relatively late in the illness as a sign of septicemia, leukocytosis and hemoconcentration. X-ray films may show signs of intestinal obstruction. The case fatality rate of untreated gastrointestinal anthrax is >50%. Prompt clinical suspicion and rapid administration of effective antimicrobials are essential for the treatment of all forms of anthrax. If untreated, all forms of anthrax can lead to septicemia and death.

Research History

The major known virulence factors of *B. anthracis* are the antiphagocytic poly- γ -D-glutamic acid capsule and the toxin (Beall et al. 1962). Anthrax toxin is composed of three proteins: protective antigen (PA), edema factor (EF), and lethal factor (LF). PA and EF comprise the edema toxin (ET) and PA and LF the lethal toxin (LT). Both of these toxins were shown to contribute to the virulence of *B. anthracis*; however, it is the LT that causes death of the infected host (Pezard et al. 1991). The genes responsible for capsular biosynthesis (Green, 1985) and the synthesis of LT and ET (Mikesell, 1983) are located on large plasmids designated pXO2 and pXO1, respectively. Welkos et al. (1988) determined the nucleotide sequence of the gene encoding PA.

A number of investigators have contributed to our understanding of how the toxin gains entry into the cell. The observation that PA blocked the action of anthrax toxin (Singh et al. 1989) suggested that they recognized a common receptor. It was subsequently shown that PA binds to the anthrax toxin receptor (ATR) (Bradley et al. 2001), is cleaved by a cell surface protease with the sequence specificity and catalytic properties of furin (Klimpel et al. 1992), and then binds LF and/or EF, facilitating internalization of these proteins into the cell (Singh et al. 1999; Friedlander, 1986). ATR is a type I membrane protein with an extracellular von Willebrand factor A domain that binds directly to PA (Bradley et al. 2001). The proteolytic activation of PA is a critical step in the membrane insertion of EF and LF

(Milne et al. 1994). The activated PA forms a multi-subunit, ring-shaped heptameric oligomer during intoxication of mammalian cells (Milne et al. 1994). Using the crystal structure of the PA monomer and oligomer, a model of pH-dependent membrane insertion involving the formation of a porin-like, membrane-spanning beta-barrel was proposed (Petosa et al. 1997). The subsequent translocation of LF and EF across the cell membrane and into the cytosol is thought to occur by a pH- and voltage-dependent mechanism (Zhao et al. 1995; Wesche et al. 1998; Blaustein et al. 1989).

EF was shown to have adenyl cyclase activity and increase cyclic AMP concentrations in eukaryotic cells (Leppla 1982). Inhibitors of receptor-mediated endocytosis blocked the entry of EF, but not that of the *Bordetella pertussis* adenyl cyclase toxin (Gordon et al. 1988).

The purification of LT has facilitated studies on its biological activity (Leppla 1988). The mechanism of action of LF inside the cell is beginning to be understood. Macrophages play a critical role in the pathophysiology of anthrax. Friedlander used an in vitro system to demonstrate that the lethality of macrophages to LT occurred through an acid-dependent process (Friedlander 1986). Systemic shock and death of the host resulted primarily from the effects of high levels of cytokines, principally IL1, produced by macrophages that had been stimulated by LT (Hanna et al. 1993). LF contains a zinc metalloprotease consensus sequence that is required for LT activity (Klimpel et al. 1994). LF cleaves the amino terminus of mitogen-activated protein kinase kinases (MAPKK/MEK), including MEK1, MEK2, MKK3, MKK4, MKK6, and MKK7 but not MKK5 inhibiting the MAPK signal transduction pathway (Duesbery et al. 1998; Pellizzari et al. 1999; Pellizzari et al. 2000; Vitale et al. 2000). In addition to cleavage of the N-terminus of MAPKKs, LF induced tyrosine/threonine phosphorylation of MAPKs in cultured macrophages (Vitale et al. 1998). However, the fact that LT-resistant and -sensitive cells show similar internalization of LF (Singh et al. 1989) and similar MEK cleavage in response to LF (Pellizzari et al. 1999; Pellizzari et al. 2000) suggests that these factors alone cannot account for differential susceptibility or resistance to LT. The completion of the genome sequence of *B. anthracis* (Read et al. 2002, 2003) will provide new insights into the pathogenesis of this microorganism.

Vaccines have played an important role in controlling anthrax. The veterinary vaccine that is currently in use in the U.S. is a spore suspension from an avirulent non-encapsulated strain (Sterne 1939). The original human anthrax vaccine was developed by George Wright in the 1950s and first produced on a large scale by Merck. Brachman et al. (1962) examined the safety of this vaccine and concluded that individual reactions to the vaccine were relatively minor. The U.S. military vaccinates at-risk personnel for anthrax in case of a biological attack. Friedlander et al. (1993) conducted a study to determine whether a prolonged course of post-exposure antibiotics, with or without vaccination, protected monkeys exposed to a lethal dose of anthrax spores when the antibiotic was discontinued. It was concluded that each

regimen completely protected animals while on therapy and provided significant long-term protection upon discontinuance of the drug. The use of the current anthrax vaccine in U.S. military personnel has become controversial due to reports of adverse reactions. A priority area for current research is the development of a better vaccine.

B. anthracis has many biological and virulence characteristics that have made it attractive as a bioweapon. In 1979, an accident occurred in a military microbiology facility in Sverdlovsk, USSR in which a small amount (less than 1 gram) of spores were released outside the facility generating an aerosol that resulted in numerous infections and at least 64 deaths (Abramova et al. 1993; Bezdenezhnykh and Nikiforov, 1980; Messelson et al. 1994). Recently, there has been considerable concern about the use of biological agents by terrorists. *B. anthracis* is one of the agents that required enhanced preparedness efforts (Franz et al. 1997; Inglesby et al. 1999). The concern about bioterrorism has been heightened in the post-9/11 era. The mailings of letters containing spores of *B. anthracis* to the media and members of the U.S. Congress in September and October of 2001 resulted in 22 cases of anthrax (11 of these were inhalational) with 5 deaths (all inhalational), closed part of the U.S. government's operations, and terrorized the American public (Jernigan et al. 2001; Hsu et al. 2002; Morse et al. 2003). Aggressive treatment enabled many of those with inhalational anthrax to survive (Inglesby et al. 2002). The investigation of this attack used a molecular typing method (variable-number tandem repeat [VNTR] analysis) (Keim et al. 2000) to identify the strain of *B. anthracis* used in the attack. Additional forensic information was provided by whole genome sequencing (Read et al. 2002). Nevertheless, the perpetrator(s) of this attack remain at large.

As a result of the renewed interest in anthrax, there have been a number of recent review articles, which provide comprehensive and complementary perspectives on this disease (Dixon et al. 1999; Mock and Fouet 2001; Gardner 2001; Khanna and Singh 2001; Oncu et al. 2003). These review articles are structured along traditional lines in that they cover the etiology and pathologic mechanisms of anthrax, addressing both biological and medical considerations. However, none of these reviews provide the infrastructure and technology structure of the anthrax literature that text mining can provide.

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